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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/611,539	07/01/2003	Bansi Lal	516745-2001.1	4710

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EXAMINER	
KOSACK, JOSEPH R	
ART UNIT	**PAPER NUMBER**
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/611,539	LAL ET AL.	
	Examiner	Art Unit	
	Joseph Kosack	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-22 and 24-26* is/are pending in the application.

4a) Of the above claim(s) *14-22* is/are withdrawn from consideration.

5)☒ Claim(s) *4,5,7,8,11 and 24* is/are allowed.

6)☒ Claim(s) *12,13,25 and 26* is/are rejected.

7)☒ Claim(s) *1-3,9 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/20/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5, 7-22, and 24-26 are pending in the instant application.

Amendments

The amendment filed on September 19, 2006 has been acknowledged and has been entered into the application file.

Information Disclosure Statement

The Information Disclosure Statement filed on September 20, 2006 has been considered fully by the Examiner. By request, the IDS filed on September 19, 2006 has been disregarded.

Previous Claim Objections

Claims 1-3, 9-10, 12-13 and 25-26 were objected to in the previous action for containing elected and non-elected subject matter. The non-elected subject matter has not been deleted completely from the claims yet, primarily the definition of X_1 and X_2. Therefore, the objections are maintained.

Previous Claim Rejections - 35 USC § 112

Claims 12-13 and 25-26 were rejected in the previous action under 35 U.S.C. 112, first paragraph as being enabling for some forms of cancer, but not all forms of cancer.

Applicant has traversed the rejection on the grounds that no evidence of inoperability for the treatment of cancer has been presented and that no evidence that the identification of inoperative elements would require undue experimentation. Applicant has submitted a declaration under 37 CFR 1.132 by Kalpana S. Joshi, an

inventor in the instant application to support the case for enablement for the treatment of cancer.

The Examiner respectfully disagrees. The test for enablement of a treatment for cancer in general is to show either in vitro or in vivo culture data translates into treatment of a suitable subject using the same target receptor site or protein.

As is shown in the IDS filed on September 20, 2006, the linkage of cyclin dependent kinases to possible cancer treatment has been known for the past decade. There are clinical trials currently to assess the viability of CDK inhibitors in cancer treatment.

In Applicant's remarks, they state that there is "overwhelming evidence in the art acknowledges that the treatment of cancers via inhibition of Cdks is well known and accepted by those of ordinary skill in the art." However, Applicant fails to point out that there has not been a single agent that will treat all cancers. Anti-cancer drugs are normally drawn to treat a particular set of cancers. For instance, the drug paclitaxel, which works by inhibiting microtubule deconstruction, is primarily used to treat ovarian cancer, breast cancer, non small-cell lung cancer in people who cannot have surgery or radiation therapy, and AIDS-related Kaposi's sarcoma. (*Bristol-Myers Squibb Patient Information for Taxol, March 2003)* The Schwartz et al: (*Journal of Clinical Oncology, 2002*, 2157-2170) article cited in the declaration and the IDS of September 20, 2006 only shows data of reduction or stable disease states for about half of the cancers tested. Those with no data as to stability or reduction that were in the sample set are: colon, rectum, liver, small bowel, melanoma, and head and neck. (Table 1, Page 2160

and Table 7, Page 2165) Since the claim encompasses all of these types of cancer, evidence must be supplied that show that inhibiting CDKs can treat these forms of cancer when in vitro and in vivo data is shown that inhibition occurs.

The Joshi declaration contains two tables on pages 6-7 that detail in vitro and in vivo data for inhibition of CDKs as well as binding to cancer cells. This data cannot be found persuasive because the tests were only conducted with one compound out of the millions of possibilities from the generic compound claim. Examples are needed for not only a broad range of cancers, but also a broad range of compounds within the generic concept as well.

The level of uncertainty in the chemotherapeutic art is still high. Uncertainty is reduced when *firm* connections between a inhibiting a receptor/protein/enzyme directly affects a specific disease state. Treating cancer is not a specific disease state. Cancer is specialized in that different types of cancer respond variably to different drugs, radiation doses, diets, and surgery. While the link between CDKs and cancer has been established, as seen by Hirama et al. (*Blood, 1995*, 841-854), different CDKs are overexpressed in different cancers. The current clinical trials of flavopiridol may shed more light on the link of a CDK to particular cancers, but as yet, there is no CDK has been shown that when inhibited, *all* cancers can be treated.

As was stated in the previous action, Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of

general ideas that may or may not be workable". The claims constitute the application for a hunting license to treat any and all diseases that may be treated by inhibiting CDKs, without showing a representative number of examples as to what is *known* to work. Undue experimentation would be needed by those of skill because only in a clinical trial will it be known whether the in vitro and in vivo data correlates to treating the disease state. This not only involves large quantities of time and money, but also requires human subjects that could possibly die from the testing. This constitutes undue risk, and therefore, undue experimentation. The rejections must currently be maintained in light of Applicant's arguments, the IDS of September 20, 2006, and the Joshi declaration.

Claim 8 was rejected under 35 U.S.C. 112, second paragraph as being indefinite. The error was corrected in the amendment of September 19, 2006, and the rejection is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-13 and 25-26 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of certain cancers, does not reasonably provide enablement for all cancers. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention are pharmaceutical compositions comprising the compound of formula 1c with a pharmaceutically acceptable carrier with the intended use for the treatment of disease mediated by inhibition of cyclin dependent kinase (Claims 12-13) or excessive cell proliferation (Claims 25-26).

The State of the Prior Art and the Predictability or Lack Thereof in the Art

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Davies et al. (*Pharmacology & Therapeutics, 2002*, 125-133) and Toogood (*Medicinal Research Reviews, 2001*, 487-498) both teach various inhibitors of CDK2 and CDK4, but show no data as to the usefulness of inhibiting these kinases as a treatment for cancer.

Hence, in the absence of a showing of correlation between all cancers claimed as capable of treatment by inhibiting cyclin dependent kinases, one of skill in the art is unable to fully predict possible results from the administration of the compound of formula 1c due to the unpredictability of the role of inhibiting cyclin dependent kinases, and the unpredictability of the ability of the compound of formula 1 to cause toxicity or any improvement in condition.

The Amount of Direction or Guidance Present and the Presence or Absence of Working Examples

The specification teaches in vitro assays done on two compounds of the instant invention with 6 different cell lines: HeLa Cervix, MCF-7 Breast, PC-3 Prostate, MDAMB-231 Breast, H460 Lung, and U-937 Histiocytic lymphoma (monocytes). If activity is to be judged by the toxicity of the compounds to the different cell lines, it seems to the Examiner that the compounds contain no activity towards MDAMB-231

Breast and H460 Lung cell lines, since the definition of "not toxic" is less than or equal to 30% toxic, which would include 0% toxicity. The compounds do contain activity to the other four cell lines, providing sufficient guidance to those of skill in the art to practice the invention to the scope of the intended use for the treatment of those specific cancers.

The Breadth of the Claims

The breadth of the claims are pharmaceutical compositions comprising the compound of formula 1c with a pharmaceutically acceptable carrier with the intended use for the treatment of all disease mediated by inhibition of cyclin dependent kinase (Claims 12-13) or excessive cell proliferation (Claims 25-26).

The Quantity of Experimentation Needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which cancers can be treated with the compounds of the instant invention, dosages, the method of drug delivery, and any potential combination therapies.

The Level of Skill in the Art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad intended use of the compound of formula 1c for the treatment of all diseases mediated by cyclin dependent kinases or excessive cell proliferation. As a result, necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of formula 1c in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome deleting the claims.

Conclusion

Claims 12-13 and 25-26 are rejected. Claims 1-3, 9-10, 12-13, and 25-26 are objected to. Claims 4-5, 7-8, 11, and 24 are held to be allowable. All examined claims are free of the art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Kosack whose telephone number is (571)-272-5575. The examiner can normally be reached on M-F 5:30 A.M. until 2:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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